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Deep Venous Thrombosis After Orthopedic Surgery in Adult Cancer Patients

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Background and Objectives: Patients with cancer and patients undergoing major orthopedic procedures are two groups at risk of deep venous thrombosis (DVT). The objective was to determine the rate of venous thromboembolic disease in patients with a malignant neoplasm and major orthopaedic surgery of the lower limb.
Methods: The study included 169 patients. All patients were given knee-high intermittent pneumatic compression devices for prophylaxis. Postoperative surveillance for thrombosis was performed on all patients with venous duplex doppler ultrasonography.
Results: Proximal DVT occurred in 24 of 169 patients (14.2%). One patient (0.6%) developed a symptomatic, nonfatal pulmonary embolus (PE). The development of DVT was not associated with age, sex, type of surgery, type of neoplasm, location, or pathologic fracture. The addition of anticoagulant medication such as warfarin did not significantly reduce the rate of DVT in a subset of 54 patients. In three patients, the DVT occurred only in the contralateral limb, and in four patients, there were bilateral DVTs.
Conclusions: When intermittent compression boots were used for prophylaxis in conjunction with ultrasound screening, the risk of proximal DVT was substantial (14.2%), but the rate of symptomatic PE was low (0.6%). *J. Surg. Oncol. 1998;68:41–47.* © 1998 Wiley-Liss, Inc.

KEY WORDS: thromboembolism; pulmonary embolus; postoperative complications; duplex doppler ultrasonography; orthopedics

INTRODUCTION

It has been generally recognized that patients with cancer are at increased risk for thromboembolic disease [1–6]. This observation has been made for many different types of tumors and malignancies, especially those involving the pelvis [7–15]. It is somewhat surprising that the problem has received scant attention in the orthopedic literature, especially in light of the strong association between various orthopedic conditions and venous thrombosis. Patients who undergo total hip and total knee replacements are at high risk for developing thromboembolic complications [16–18]. Without prophylaxis, the overall rate of thromboembolic events has been estimated to be 45–69% for total hip replacement [16,19–23] and 52–84% for total knee replacement [24–29]. The rate of pulmonary emboli has been reported to be 3.2–23% for hip replacement [16,17,30–33] and 2.7–24% for knee replacement [32–35]. Patients who have hip, pelvic, and acetabular fractures are also notably at high risk for thromboembolic disease with overall rates of deep ve-

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nous thrombosis ranging from 39–75% [21,36–42]. It has thus been assumed that orthopedic patients with malignant disease would be at the highest risk of thromboembolism [5].

Patients with musculoskeletal tumors have the potential for fulfilling Virchow's classic triad. (1) The neoplastic process may liberate factors that affect the clotting process and induce hypercoagulability [1,43,44]. (2) Circulatory stasis is induced by bulky tumors, decreased mobility, long operation times, and unnatural positioning of limbs during surgery. (3) Pathologic fractures and surgical trauma can each lead to endothelial damage.

Although it seems plausible that patients with neoplasms undergoing orthopedic surgery would be at increased risk for deep venous thrombosis, there has been no study that attempts to quantify the magnitude of the problem or assess the adequacy of current methods of prophylaxis. The lack of published data probably stems from the numerous and substantial difficulties in studying this problem. Primary musculoskeletal tumors are rare, and it is not easy to obtain sufficient numbers of patients for a meaningful study. The population of patients with orthopedic neoplasms is heterogeneous, and there is a wide variety of lesions, locations, procedures, ages, and other patient characteristics involved. Finally, there have been no previous studies on the natural history of DVT in these patients, which precludes the possibility of using historical controls to measure the effectiveness of current methods of prophylaxis.

The goal of the present study is to determine the prevalence of DVT in patients with neoplasms who undergo orthopedic surgery and receive basic prophylaxis in the form of pneumatic compression stockings. The study focuses on the patients who seem most at risk for developing thrombosis—those with active malignant neoplasms who undergo major procedures on the pelvis or lower limbs. Specific characteristics of patients are examined to determine whether certain subsets are at higher risk of thrombosis.

MATERIALS AND METHODS

Study Design

A prospective study was undertaken to evaluate the rate of DVT in cancer patients undergoing major musculoskeletal surgery of the lower limbs. All 169 patients in the study were treated at this institution between June 1994 and August 1996. A protocol for DVT prophylaxis and screening was established at the beginning of the study (see below).

Patients

Patients had to satisfy the following criteria for inclusion in the study. Age was 21 years or older. Major musculoskeletal surgery was performed on the pelvis or lower limbs. The procedure had to result in significantly diminished mobility and require hospitalization of at least 4 days. An active malignant neoplasm had to be present at the time of surgery. Patients who had a previous history of cancer but no detectable disease at the time of surgery were not included.

Patients were excluded for the following reasons: (1) minor operations, such as simple biopsies, (2) a previously placed inferior vena caval filter, (3) diagnosis of a DVT prior to surgery, (4) no detectable malignant disease at the time of operation, (5) an impediment to obtaining a venous ultrasound scan, such as brachtherapy catheters or a cast, and (6) amputation. Patients who underwent amputations were excluded since they were expected to have thrombosis at the level of the divided vein.

Of the 193 patients who met eligibility requirements, 169 patients were included in the study. The remaining 24 patients were not included because they did not have a postoperative ultrasound scan. Ninety-five females and 74 males were entered into the study. Ages ranged from 21 yr to 92 yr with a mean of 59.7 yr. A total of 103 patients had metastatic disease to the surgical site; 50 patients had primary or locally recurrent tumors; and 16 patients had concurrent neoplasms that did not directly involve the surgical site.

Protocol for DVT Prophylaxis and Management

Prior to surgery, all patients were examined carefully for signs of venous thromboembolism. Seventeen patients were studied with pre-operative duplex doppler ultrasonography, and six patients were found to have a DVT. These patients were treated with inferior vena caval filters and excluded from the present analysis.

Patients were given knee-high pneumatic intermittent compression devices (7 Venodyne, Advanced Instruments, Norwood, MA) during and after surgery. The device inflated to 30–40 mm Hg for 12 sec, then deflated for 48 sec, thus cycling once every minute. During surgery, the sleeve was placed only on the uninvolved extremity. After surgery, the sleeves were worn constantly, and they were placed on both extremities whenever feasible. Intermittent compression was continued until the ultrasound scan results were known and the patient ambulatory. All data are based upon intent to treat with intermittent compression boots and not on strict compliance with wearing the boots.

Fifty-four patients received anticoagulant medications in addition to intermittent compression devices postoperatively. The decision to give the medications was made on a case-by-case basis at the discretion of the attending physician. The administration of all anticoagulant medications was carefully monitored, and complete data on these medications was verified against hospital pharmacy computer records.

All patients were screened for postoperative DVT (see below). Patients who were diagnosed with venous throm-

boembolism were treated acutely with an intravenous heparin infusion. Patients were subsequently managed with either an inferior vena caval filter and/or oral warfarin for a total of 3 mo.

Screening for Venous Thromboembolism

Duplex ultrasound scans were performed on all patients between the fourth and seventh postoperative day. The timing of the scans varied since they were not routinely available on weekends. Pulmonary ventilation-perfusion scans were performed only on symptomatic patients suspected of having a pulmonary embolism. Routine surveillance lung scans were not performed.

According to American College of Radiology protocol standards [45], ultrasonography was performed from the saphenofemoral junction to the popliteal trifurcation to include the common femoral vein, origin of the deep femoral vein, superficial femoral vein, and popliteal vein. Calf veins were not routinely evaluated. Studies were performed with standard compression and doppler technique as described by Cronan et al. [46] and all studies were monitored by an experienced radiologist. Venous thrombosis was diagnosed when veins were noncompressible. Only DVTs in the femoral-popliteal system were scored as positive. Thromboses of superficial veins, such as the saphenous vein, and calf veins were not counted as DVTs.

Statistics

All data were entered into an Excel (8 Microsoft Corporation) database and then transferred to SPSS (8 SPSS) for statistical analysis. The Chi-square test was used to compare the various groups with respect to occurrence of DVT. Fisher's exact test was used for small numbers (i.e., when the expected frequency of a cell in a 2×2 table was <5). The student's *t*-test was used to compare the means of the ages of patients with and without DVT. Statistical significance was defined as $P < 0.05$. Correlative studies were performed separately upon patients who received supplemental chemical anticoagulation and those who did not. Since there were no differences between the groups in any of the demographic or treatment factors analyzed, the analysis is presented for the entire study population.

RESULTS

Of the 169 patients who underwent postoperative venous ultrasonography, 22 patients had a positive scan for a deep proximal DVT in the immediate postoperative period between the fourth and seventh day. Two additional patients had negative scans initially but developed symptomatic DVTs subsequently, one at 1 mo and one at 3 mo. Both of these DVTs were considered to be postoperative DVTs. Thus a total of 24/169 patients (14.2%) were found to have a proximal deep DVT. Three patients had a DVT isolated to the contralateral limb, and four patients had bilateral DVTs, making a total of 7/24 patients (29% of the patients with DVTs) who had a remote thrombus away from the surgical side.

TABLE I. Postoperative Deep Venous Thrombosis (DVT) in Adults With Cancer Undergoing Orthopedic Surgery: Location of Surgery and Occurrence of DVT

Location	No. of patients	No. of patients with DVT	% DVT
Pelvis and sacrum	30	5	16.7
Proximal femur and hip	96	11	11.5
Mid femur and thigh	19	3	15.8
Distal femur and knee	16	4	25.0
Tibia, fibula, and calf	8	1	12.5

Most patients with DVTs were treated initially with an intravenous heparin infusion. An inferior vena caval filter was placed without complication in nine patients. The other patients were treated with oral warfarin. One of the patients on warfarin developed a symptomatic PE on the sixth postoperative day. The lung scan showed a ventilation-perfusion mismatch, which was interpreted as highly probable for a PE. This patient continues to be alive 2 yr and 1 mo after surgery. The overall prevalence of symptomatic, perioperative PE in this series was 0.6%.

The occurrence of a DVT was not associated with gender. Twelve of 74 males (16.2%) and 12 of 95 females (12.6%) developed a DVT ($P = 0.52$, two-tailed test). The presence of a fracture did not significantly increase the risk of a DVT. Eight of 60 patients (13.3%) with a fracture had a DVT, whereas 16 of 109 patients (14.7%) without a fracture developed a DVT ($P = 0.81$, two-tailed test). No single location of surgery was associated with a significantly increased or decreased rate of DVT (Table I).

Age was not associated with the presence of a DVT ($P = 0.48$, two-tailed test). The mean age of patients with DVTs was 61.5 ± 12.3 standard deviation (S.D.) yr, and the mean age of patients without DVTs was 59.4 ± 13.4 yr. The youngest patient to have a DVT was 38 yr old. None of the 12 patients between 21 and 38 had a DVT, but this was not statistically significant ($P = 0.15$, one-tailed test).

The most common operative procedures are listed in Table II. The risk of postoperative DVT was not significantly increased or decreased for any single procedure. For total knee replacements, which had the highest rate of DVTs, 4 of 16 patients (25%) developed DVTs ($P = 0.25$, two-tailed test).

The most common pathologic diagnoses are listed in Table III. Again, the risk of DVT was not significantly increased or decreased for a particular diagnosis. Chondrosarcoma was associated with the highest rate of DVT (5 of 18 patients [27.8%]), but this was not statistically significant ($P = 0.14$, two-tailed test). Although none of

TABLE II. Postoperative Deep Venous Thrombosis (DVT) in Adults With Cancer Undergoing Orthopedic Surgery: Rate of CVT for Different Procedures

Procedure	No. of patients	No. of patients with DVT	% with DVT
Internal hemipelvectomy	11	2	18.2
Total hip replacement	23	2	8.7
Hip hemiarthroplasty	83	10	12.0
Total knee replacement	16	4	25.0
Soft tissue	15	3	20.0
All other procedures	21	3	14.3

TABLE III. Postoperative Deep Venous Thrombosis (DVT) in Adults With Cancer Undergoing Orthopedic Surgery: Effect of Pathologic Diagnosis

Diagnosis	No. of patients	No. of patients with DVT	% with DVT
Breast	35	5	14.3
Sarcoma[a]	32	5	15.6
Chondrosarcoma	18	5	27.8
Lung	16	3	18.8
Prostate	16	1	6.3
Renal	13	3	23.1
Multiple myeloma	11	0	0
All other	28	2	7.1

[a]Other than chondrosarcoma.

the 11 patients with multiple myeloma had a DVT, this also was not statistically significant ($P = 0.37$, two-tailed test).

Patients were analyzed from the perspective of whether they had primary, metastatic, or concurrent lesions (Table IV). Concurrent lesions included cases such as nonpathologic fractures in patients with cancer. Locally recurrent tumors were combined with primary tumors. There was not a statistically significant relationship between these categories and the occurrence of a DVT ($P = 0.37$, two-tailed test).

A total of 54 patients received some form of anticoagulation postoperatively (Table V). Seventeen patients received low dose warfarin, and 32 received subcutaneous heparin. One patient received low-molecular dextran for a vascular repair, and four patients received aspirin. The administration of anticoagulant medication was not associated with a significantly reduced risk of DVT when compared to patients who received only pneumatic intermittent compression. Postoperative DVTs occurred in 7 of 54 patients (13.0%) who received both intermittent compression and anticoagulant medication and 17 of 115 patients (14.8%) who received only pneumatic intermittent compression ($P = 0.48$, one-tailed test). Only one of 17 patients (5.9%) who received warfarin and intermittent compression developed a DVT, but this was not significantly different from patients who received intermittent compression only ($P = 0.29$, one-tailed test).

TABLE IV. Postoperative Deep Venous Thrombosis (DVT) in Adults With Cancer Undergoing Orthopedic Surgery: Effect of Type of Lesion

Type of lesion	No. of patients	No. of patients with DVT	% with DVT
Primary or recurrent[a]	50	10	20.0
Concurrent	16	2	12.5
Metastatic	103	12	11.7

[a]Locally recurrent in the same site as original primary tumor.

TABLE V. Postoperative Deep Venous Thrombosis (DVT) in Adults With Cancer Undergoing Orthopedic Surgery: Effect of Anticoagulant Medications

Medication	No. of patients	No. of patients with DVT	% with DVT
None	115	17	14.8
Warfarin	17	1	5.9
Heparin	32	5	15.6
All other	5	1	20.0

Thirty-five patients died during the period of follow-up. Six of these patients were known to have a DVT. There was not a statistically significant relationship between death and the occurrence of a DVT ($P = 0.37$, one-tailed test). Of the 13 patients who died within 3 mo of surgery, one was known to have a DVT, and this was not statistically significant ($P = 0.42$, one-tailed test).

DISCUSSION

Little information is available on DVTs in cancer patients having orthopedic surgery despite the widely held notion that such patients would be at increased risk of venous thromboembolism. This is a difficult subject to study since orthopedic oncology encompasses the treatment of many diverse and rare disorders. Consequently, there have been no studies on the natural history of DVTs in this patient population, and it is not known what the rate of DVT would be without prophylaxis. It is also not known what form of prophylaxis would be most appropriate for these patients. Although anticoagulant medications are widely used in orthopedic patients, the medications may not be ideal for debilitated patients who sustain considerable blood loss during surgery.

The goal of the present study was to determine the rate of proximal DVT with pneumatic compression boots. This form of prophylaxis has been shown to have some efficacy with essentially no risk of serious complications [26,34,47–51]. The devices are widely used and applicable to nearly all patients. Even in cases where postoperative dressings and splints interfere with the device, there has been reported beneficial systemic effect from placing the device on an uninvolved extremity [52–54].

The study would have benefitted from inclusion of a placebo control to assess the efficacy of the pneumatic

compression boots, but such a study design is difficult to justify from both an ethical and legal standpoint because of the potential catastrophic outcome of thromboembolism and the prevailing concept that cancer patients are at high risk for thromboembolic disease [1–6]. Current practice guidelines by the state Physician Review Organization dictate that all hip and knee replacement and other high-risk patients must receive prophylaxis against DVT.

The prevalence of proximal DVT in this series was 14.8% (17/115) for compression boots alone. The figure is relatively high when compared to other orthopedic series employing external pneumatic compression, which have reported rates of proximal DVT ranging from 6–15% [49–51,55–58]. Since ultrasound was used for diagnosis, the rate of DVT reported here is probably a conservative estimate, and the true rate is likely to be even higher. Duplex doppler ultrasound has certain advantages, including noninvasiveness, portability, and relatively low cost [46,59–62]. The specificity is excellent and approaches 97–100% for proximal DVTs [63–66]. However, a recent meta-analysis has shown that the overall sensitivity in well-controlled studies is only 79% for postoperative orthopedic patients [65]. It has also been observed that the accuracy of the test depends on the experience and skill of the operator [67].

Despite the substantial rate of DVT with compression boots alone, the rate of symptomatic PE was low (0.6%) in this series. The paucity of PEs may be attributable in part to the screening protocol for DVT, which included a preoperative clinical evaluation, doppler scans on symptomatic preoperative patients, and surveillance doppler scans on all postoperative patients. Whereas boots may be only moderately effective in this patient population, careful screening may help improve the ultimate outcome by reducing the risk of major, symptomatic PE.

The occurrence of subclinical, small PEs may have escaped detection since only symptomatic patients were studied with lung scans. However, there was no indication that undetected thromboembolic disease had an impact on outcome, and a statistically significant relationship could not be found between the occurrence of DVT and postoperative death. Of the 13 patients who died during the first 3 mo after surgery, only one was known to have had a DVT. Nevertheless, since autopsies were not routinely performed, it is not certain whether thromboembolism contributed to these patients' death.

Anticoagulant medications are effective prophylactic agents, but are associated with hemorrhagic and other complications [30,68–76]. Patients with tumors often have abnormalities of coagulation that promote bleeding and consumption of clotting factors [77,78]. Due to high blood loss and the frequent necessity to operate through highly vascular tissue planes, the patients in this study were expected to have a greater risk of postoperative bleeding and wound complications than nononcologic orthopedic patients. Consequently, most patients in this study were managed with compression boots alone.

Fifty-four patients received anticoagulation postoperatively. No significant difference in the rate of DVT was found between patients that received anticoagulant medications and those that had pneumatic compression devices only. The data can be interpreted several ways. Chemical anticoagulation may have added no protection against DVT beyond that of intermittent compression alone. Alternatively, there may have been selection bias in the choice of patients to receive chemical prophylaxis, and this may have masked the effect of anticoagulation. Finally, there may have been insufficient numbers of patients to detect a significant difference. Clearly, more work is needed to define further the role of chemical prophylaxis for these patients.

The analysis demonstrated that no particular diagnosis, procedure, or characteristic was associated with a significantly higher or lower rate of DVT. Therefore, all cancer patients having major orthopedic surgery of the pelvis or lower extremities should be considered to be at substantial risk of thromboembolic disease, and a high index of suspicion should be maintained for all patients. It is possible that with a larger sample size, certain subsets of patients eventually may be found to have greater or less risk of DVT, and this may have an impact upon the choice of prophylaxis for that particular group of patients.

An interesting observation was that three patients had DVTs isolated to the contralateral limb and four additional patients had bilateral DVTs. Thus a total of seven of 24 patients (29%) had a proximal thrombus away from the site of surgery. The finding supports the notion that in addition to local, mechanical factors that promote the formation of DVT, there are also systemic factors that stimulate thrombosis in cancer patients. The finding supports the use of bilateral ultrasound examinations for screening as opposed to unilateral scans in this patient population.

CONCLUSIONS

The overall prevalence of proximal, postoperative DVT was 14.8% with compression boots alone. It is not known which cancer patients undergoing major lower extremity orthopedic procedures may require chemical prophylaxis for DVT. Any decision must be balanced against the hemorrhagic and general risks in this debilitated population. There was no clinical subset of patients that was at significantly less or greater risk than other patients, and thus a high index of suspicion should be maintained for all patients. When compression boots were used in conjunction with a screening program that included routine surveillance postoperative ultrasound scans, the rate of symptomatic PE was 0.6%.

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